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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | | ATTORNEY DOCKET NO. |
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| 09/617,569 | 07/17/00 | ROELVINK | P | 204133 |

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| EXAMINER | |
|---|---|
| FOLEY,S | |
| **ART UNIT** | **PAPER NUMBER** |
| 1648 | 8 |

**DATE MAILED:** 03/07/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trad marks**

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/617,569 | ROELVINK ET AL. | |
| | Examiner | Art Unit | |
| | Shanon A. Foley | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-43 is/are pending in the application.

4a) Of the above claim(s) 33-39 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-32 and 40-43 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

## DETAILED ACTION

### *Election/Restriction*

Claims 33-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Applicant argues that that even though the inventions are distinct and independent, it would be less burdensome than searching the inventions separately. Applicant states that some of the Group II claims are dependent on the claims in Group I and that the complexes in Group II concern the complexes recited in Group I.

The arguments have been considered and are not found persuasive because the claims in Group II are directed to a library, which has an infinite number of complexes, a few of which have been recited in Group I. The majority of the remaining complexes contained in the library of Group II, are not described in the application in such a way that would imply that every complex contained in the library has been found relevant to the claimed invention and matches the claim limitations concerning the complexes in Group I. In addition, the claims in Group II are drawn to an entirely different class and subclass, another indication of a divergent search and more evidence that a search burden has been established. Claims 1-32 and 40-43 are under consideration.

### *Claim Objections*

Claim 20 is objected to because of the following informalities: The claim recites "the animal mounds..." It is assumed that "mounds" should be "mounts". Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is drawn to the complex of claim 1 comprising a liposome. This claim is vague and indefinite because it is not clear whether the liposome is a separate entity in a composition comprising the complex of claim 1, or whether the liposome comprises the virion with non-native ligands and the ligands are protruding from the liposome.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-32 and 40-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a complex comprising a virion that contains a non-native ligand and a non-native antigen. The nature of the invention is to utilize the complex to elicit an immune response against the foreign antigen(s) that is incorporated in the virion. The non-native ligand is a ligand that recognizes CD-40 or osteopontin on an antigen-presenting cell. Once ligand binding has occurred, the liposome facilitates viral integration into the host membrane.

The combination of the virus' natural viral capsid proteins and the foreign antigen elicit a MHC I and II response against the foreign antigen(s).

The state of the art at the time the invention was made for using an anti-CD40 ligand in combination with a recombinant adenovirus (Ad) is demonstrated by Stein et al. The teachings of Stein et al. demonstrate that the anti-CD40 ligand reduced the immune response. Stein et al. teaches there is normally rapid elimination of transgene expressing cells shortly after administration of the Ad-containing transgene. In addition, a natural generation of neutralizing antibodies against the Ad capsid proteins correlates with the inability to readminister the vector. The purpose of administering an anti-CD40 ligand in addition to the adenovirus vector was to depress the immune response to prolong transgene expression and permit redosing of recombinant Ad, see the abstract and the first paragraph of the introduction. Stein et al. also teaches that mice treated with anti-CD40 display poor T cell-dependent antibody responses. Based on the teachings of Stein et al., one skilled in the art at the time the invention was made would have doubt that administering an anti-CD40 would aid in up-regulating an immune response.

Yu et al. teaches the state of the art at the time the invention was made for administering osteopontin. Yu et al. teaches that osteopontin demonstrated no effect on humoral immune response and was accompanied by a significant reduction in T-cell activation and accumulation, see the abstract.

There are no working examples provided in the specification that utilize the claimed composition or any working examples demonstrating its effect in a pharmaceutical composition. Although one skilled in the art would have little doubt that anti-CD40 would successfully target

immune effector cells, the state of the art at the time the invention was made teaches that the immune system is negatively effected by anti-CD40 and osteopontin, which is the opposite goal intended by the inventors. There is no teaching in the art, or in the specification, that demonstrates that the addition the stimulating effects of a liposome and foreign antigen in a viral vector, would counteract the negative effects of an anti-CD40 ligand with the addition of any cytokine. Therefore, due to the state of the art teaching the negative effects anti-CD40 on the immune system and the lack working examples or guidance in the specification on the predictability of up-regulating the immune response while using the anti-CD40 ligand to target immune effector cells, it is determined that undue experimentation by one skilled in the art would be required to practice the claimed invention.

Claims 1-32 and 40-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vector comprising a non-native ligand, a non-native antigen, and a cytokine, does not reasonably provide enablement for a vector comprising any cytokine to mount an immune response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Each cytokine has multiple activities, demonstrated in Figure 7.31 of Immunobiology by Janeway et al. on page 7:27. The nature of the invention is directed to stimulating the immune system. Therefore, the scope of specific cytokine used to practice the invention should be limited to only those cytokines that activate the immune system, like INF-$\gamma$, TNF-$\beta$ and TNF-$\alpha$. Cytokines that do not elicit an immune response, such as IL-4, IL-10, and TGF-$\beta$ are excluded from the scope of the invention.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4-7, 9, 11-16, 19, 26, 27, 40, 42, and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Wickham et al. in U.S. Patent 5,846,782.

The claims are drawn to a complex comprising a virion that has a non-native ligand that recognizes an epitope on an immune effector cell, an RGD motif, and a non-native antigen. The non-native antigen is a gene product from a pathogen or a malignant cell. The virion comprises a chimeric protein where the first protein is from an adenovirus capsid protein and the second domain is a ligand, and elicits less specific immunogenicity than the wild-type virus. The complex is inoculated by a pharmaceutical carrier to elicit an immune response.

Wickham et al. teaches a recombinant adenovirus that has a chimeric adenovirus fiber protein comprising an RGD motif, see claims 1-3, 8, 19, 20, and 24; column 6, lines 28-53 and column 9, lines 29-45. Wickham et al. also teaches the incorporation of a passenger gene, such as HSV thymidine kinase, see column 14, lines 37-59. The passenger gene can elicit a strong immune response, resulting in a therapeutic effect, including a vaccination that can be inoculated, see column 14, lines 37-59, column 19, lines 19-38, and column 20m, lines 12-26. Wickham et al. also describes gene delivery mediated by adenovirus vectors having insertions of various peptide motifs of the adenovirus fiber protein.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wickham et al. as applied to claims 1, 2, 4-7, 9, 11-16, 19, 26, 27, 40, 42, and 43 above, and further in view of Hitt et al.

See the teachings of Wickham et al. above. Wickham et al. does not teach a second non-native antigen that is the same as the second non-native antigen to be incorporated into the complex or a liposome.

Claim 10 is drawn to the complex incorporating a liposome. Wickham et al. does not explicitly teach incorporation of a liposome. However, liposomes are used as a conventional means in the art to stimulate the immune system and facilitate fusion of the target cell membrane with the complex.

Hitt et al teaches that up to 8.3 kbp of foreign DNA can be inserted in an adenovirus genome without sacrificing any of the wild type Ad sequences, see the paragraph bridging pages 15-17. The teachings of Hitt et al. demonstrates a common knowledge in the state of the art at the time the invention was made that any number of foreign genes can be inserted into an adenovirus without destroying any part of the viral genome. The teachings of Hitt et al. suggest that one skilled in the art would have more than a reasonable expectation of success in expressing a numerous genes an adenovirus without destroying any of the viral genome.

Therefore, teachings of Wickham et al. in view of Hitt et al. renders claims 8 and 10 obvious to one of ordinary skill in the art at the time the invention was made.

Claims 18, 20-23, 25, 28-30, 32, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wickham et al. and Hitt et al. as applied to claims 1, 2, 4-16, 19, 26, 27, 32, 40, 42, and 43 above, and further in view of Janeway et al.

See the teachings of Wickham et al. and Hitt et al. above. Neither reference teaches the second antigen in the complex as a cytokine, nor do the references teach the effect of the MHC I and II responses to the complex.

Janeway et al. teaches a number of cytokines and their effect on the immune response. Figure 7.31 on page 7:27 teaches that INF-γ activates MHC classes I and II. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate INF-γ into the immune complex as the second non-native antigen into the complex in order to achieve a natural immune response by activating MHC I and II. In addition, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because of the natural characteristic of the interferon to invoke a strong immune response.

Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 7:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
March 2, 2001

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800
1600